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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/620,840	07/16/2003	Karen Duff	1310.002US1	8787

21186 7590 03/31/2006

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EXAMINER

CHEN, SHIN LIN

ART UNIT PAPER NUMBER

1632

DATE MAILED: 03/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/620,840

Applicant(s)

DUFF, KAREN

Examiner

Shin-Lin Chen

Art Unit

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 March 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-19 is/are pending in the application.
- 4a) Of the above claim(s) 4-6, 13-16, 18 and 19 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3, 7-12 and 17 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 20 January 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 7-5-05.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse of group I, claims 1-3, 7 and 10-12, in the reply filed on 3-22-06 is acknowledged. The traversal is on the ground(s) that the inventions are closely related, groups I and II have same class and subclass, and there is no serious burden to search and examine groups I and II since groups I and II can be efficiently and effectively searched in a single search. This is not found persuasive because groups I and II are drawn to transgenic mice having DNA sequences that differ in chemical structures and biological functions: wild type human genomic sequence encoding tau vs. mutated human DNA sequence encoding mutated tau. The transgenic mice of group I and II differ phenotypically and physiologically because the DNA used to make said transgenic mice are different. Search for group I does not require search for group II. There is serious burden to search both groups I and II. Thus, groups I and II require separate search and are patentably distinct from each other. Groups I-II, group III and group IV are patentably distinct from each other because they are drawn to materially different methods that differ in objectives, method steps, dosages and reagents used, schedules used, response variables, and criteria of success. They have different classifications and require separate search. Thus, groups I-IV require separate search and searching groups I-IV would impose serious search burden on examiner.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 4-6, 8, 9 and 13-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 3-22-06.

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Applicant's preliminary amendment filed 1-20-04 has been entered. Since claims 8, 9 and 17 read on the expressed human tau isoforms that are wild-type tau, i.e. no mutation, but they have abnormal conformation, therefore, claims 8, 9 and 17 will join group I and will be examined. Claims 1-19 are pending. Claims 1-3, 7-12 and 17 are under consideration.

Specification

3. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet **within the range of 50 to 150 words**. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The abstract submitted on page 35 only has 17 words. Appropriate correction is required.

Oath/Declaration

4. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
It does not identify the citizenship of each inventor.

The citizenship of the inventor Karen Duff is missing.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 10-12 and 17 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 35, 41, 42, 44 and 49 of copending Application No. 10/226,089. Although the conflicting claims are not identical, they are not patentably distinct from each other because although drawn to different scope, they encompass the same invention and obvious variants thereof.

Claims 10-12 and 17 of the instant invention are directed to a transgenic mouse whose genome stably comprises a human genomic DNA sequence comprising a human tau promoter and a DNA sequence encoding human tau, wherein said DNA sequence comprises one SrfI restriction site in the tau coding region and the transgenic mouse expresses six isoforms of the human tau and the ratio of the six isoforms is altered in the transgenic mouse relative to the ratio

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in human, the progeny of said transgenic mouse, and a method of expressing human tau in a mouse. Claim 17 specifies the human tau isoform has an abnormal conformation.

Claims 35, 41, 42, 44 and 49 of Application No. 10/226,089 ('089) are directed to a transgenic mouse whose genome stably comprises a human genomic DNA sequence comprising a human tau promoter and a DNA sequence encoding human tau, wherein said DNA sequence comprises one SrfI restriction site in the tau coding region and the transgenic mouse expresses six isoforms of the human tau, the progeny of said transgenic mouse, and a method of expressing human tau in a mouse. Claims 41 and 49 specify at least one human tau isoform has an abnormal conformation.

Since both the instant invention and '089 use the human genomic DNA sequence comprising a human tau promoter and coding sequence having a SrfI restriction site to generate the transgenic mouse, it would have been obvious for one of ordinary skill that the expression of the six isoforms of human tau in the transgenic mouse disclosed by '089 would have altered ratio of the six isoforms. Thus, claims 10-12 and 17 of the instant invention would be obvious to one of ordinary skill in the art at the time of the invention according to the teaching of '089.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 101

6. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 10-12 and 17 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

Claims 10-12 and 17 are directed to a transgenic mouse whose genome stably comprises a human genomic DNA sequence comprising a human tau promoter and a DNA sequence encoding human tau, wherein said DNA sequence comprises one SrfI restriction site in the tau coding region and the transgenic mouse expresses six isoforms of the human tau and the ratio of the six isoforms is altered in the transgenic mouse relative to the ratio in human, the progeny of said transgenic mouse, and a method of expressing human tau in a mouse. Claim 17 specifies the human tau isoform has an abnormal conformation.

The specification only discloses generation of genomic human-tau transgenic mice 8c and 5d that express all six human tau isoforms, the expression of human tau in neurites and at synaptic terminals, more 3-repeat containing human tau present in the genomic transgenic mouse brain as compared to human, and detection of human tau having abnormal conformation in the genomic human-tau transgenic mice (e.g. p. 18-20). The specification states that “[n]o motor abnormalities or abnormal pathology has been observed in the spinal cords of 8c or 5d mice up to 8 months of age (p. 18, lines 27-29), and “hind-limb clasping and spinal cord abnormalities were not observed in the genomic mice at ages up to eight months (oldest age studied)” (p. 21, lines 3-5).

The claims encompass transgenic mouse whose genome comprises a human genomic DNA sequence encoding the human tau isoforms and the six isoforms of human tau are

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expressed and the ratio of the six isoforms is altered in said transgenic mouse relative to the ratio in human. The expression of six human tau isoforms, the more 3-repeat containing human tau, and the presence of human tau having abnormal conformation fail to provide specific and substantial utility for the claimed genomic human-tau transgenic mice. In fact, the specification states that “[N]o motor abnormalities or abnormal pathology has been observed in the spinal cords of 8c or 5d mice up to 8 months of age”, and “hind-limb clasping and spinal cord abnormalities were not observed in the genomic mice at ages up to eight months”. There is no correlation of the expression of six human tau isoforms, the more 3-repeat containing human tau, and the presence of human tau having abnormal conformation with any particular disease or disorder, such as Alzheimer’s disease, FTDP-17 or Parkinson’s disease. Further, the specification also fails to provide any altered ratio of the human six tau isoforms in the transgenic mouse other than the more 3-repeat containing human tau as disclosed. One skilled in the art at the time of the invention would not know what kind of altered ratio of the expressed human tau six isoforms would be and the correlation between the altered six isoforms and a particular disease and disorder, such as Alzheimer’s disease, FTDP-17 or Parkinson’s disease, has not been established. A substantial utility is a utility that defines a “real world” use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a “real world” context of use are not substantial utilities. Absent the correlation between a phenotype of the claimed genomic human-tau transgenic mice and a particular disease or disorder, such as Alzheimer’s disease, no “real world” use of the claimed transgenic mice has been established. The asserted utility for the claimed non-human mammals for studying the biology of tau in vivo and to generate suitable animals for disease modeling (p. 21, lines 23-24) does not appear to be

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specific and substantial because no correlation between the claimed transgenic mouse and any particular disease or disorder, such as Alzheimer's disease, FTDP-17 or Parkinson's disease etc., has been established, and utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. Thus, the specification fails to support and provide evidence for a specific and substantial utility or a well-established utility for the claimed genomic human-tau transgenic mice.

Claims 10-12 and 17 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 2, 3, 7, 10-12 and 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the generation of hTau mice by crossing genomic human-tau transgenic mice 8c with a knockout mouse that does not express mouse tau, wherein the hTau mice show an accumulation of abnormal tau in the cell bodies and dendrites of neurons in the hippocampal, neocortex and brainstem, does not reasonably provide enablement for a transgenic mouse whose genome express six isoforms of human tau but not express endogenous murine tau, and said mouse develops various types of spinal cord pathology, any motor

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abnormality, any dementing disorder or various types of neurodegenerative disorder, or a transgenic mouse whose genome express six isoforms of human tau with various altered ratio of the six isoforms in said transgenic mouse relative to the ratio in human. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 2, 3 and 7 are directed to a transgenic mouse whose genome stably comprises a human genomic DNA sequence comprising a human tau promoter and a DNA sequence encoding human tau, wherein said DNA sequence comprises one SrfI restriction site in the tau coding region and the transgenic mouse expresses six isoforms of the human tau and does not express endogenous murine tau, and wherein the transgenic mouse accumulates filamentous tau in dendrites of hippocampal neurons. Claims 2 and 3 specify the transgenic mouse develops abnormal cord pathology and has motor abnormalities, respectively. Claim 7 specifies the transgenic mouse has a dementing disorder or a neurodegenerative disorder. Claims 10-12 and 17 are directed to a transgenic mouse whose genome stably comprises a human genomic DNA sequence comprising a human tau promoter and a DNA sequence encoding human tau, wherein said DNA sequence comprises one SrfI restriction site in the tau coding region and the transgenic mouse expresses six isoforms of the human tau and the ratio of the six isoforms is altered in the transgenic mouse relative to the ratio in human, the progeny of said transgenic mouse, and a method of expressing human tau in a mouse. Claim 17 specifies the human tau isoform has an abnormal conformation.

The specification discloses generation of genomic human-tau transgenic mice 8c and 5d that express all six human tau isoforms, the expression of human tau in neurites and at synaptic

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terminals, more 3-repeat containing human tau present in the genomic transgenic mouse brain as compared to human, and detection of human tau having abnormal conformation in the genomic human-tau transgenic mice (e.g. p. 18-20). The specification further discloses the generation of hTau mice by crossing genomic human-tau transgenic mice 8c with a knockout mouse that does not express mouse tau. The hTau mice show an accumulation of abnormal tau in the cell bodies and dendrites of neurons in the hippocampal, neocortex and brainstem by 3 months, and tau in hTau mice is reactive with antibodies specific to phosphorylation and conformation changes associated with Alzheimer's disease, including phosphorylation at S202 and T231, and MC1 conformation (e.g. p. 22, lines 9-21).

Claims 2, 3 and 7 encompass any transgenic mouse whose genome express six isoforms of human tau but not express endogenous murine tau, and said mouse develops various types of spinal cord pathology, any motor abnormality, any dementing disorder or various types of neurodegenerative disorder. Claims 10-12 and 17 encompass any transgenic mouse whose genome express six isoforms of human tau and the ratio of the six isoforms is altered in said transgenic mouse relative to the ratio in human.

The specification fails to provide adequate guidance and evidence for how to make and/or use a transgenic mouse whose genome express six isoforms of human tau but not express endogenous murine tau, and said mouse develops various types of abnormal spinal cord pathology, any motor abnormality, any dementing disorder or various types of neurodegenerative disorder. No phenotype of abnormal spinal cord pathology, motor abnormality, any dementing disorder or any neurodegenerative disorder has been disclosed in the claimed transgenic mouse. The specification also fails to provide adequate guidance and evidence for how to make and/or

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use a transgenic mouse whose genome express six isoforms of human tau and said mouse has altered ratio of the six isoforms other than the more 3-repeat containing human tau present in the genomic transgenic mouse brain relative to the ratio in human as disclosed. No phenotype of various altered ratio of the human six tau isoforms in the transgenic mouse other than the more 3-repeat containing human tau has been disclosed and the correlation between the altered six isoforms and a particular disease and disorder, such as Alzheimer's disease, FTDP-17 or Parkinson's disease, has not been established. Absent the phenotype of the claimed transgenic mouse, one skilled in the art at the time of the invention would not know how to use the claimed transgenic mouse.

It also should be noted that the art of transgenics at the time of filing held that the phenotype of transgenic animal was unpredictable. Kappel et al., 1992 (Current Opinion in Biotechnology, Vol. 3, p. 548-553, IDS) reports that the individual gene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct, the site of integration, etc., are the important factors that governs the expression of a transgene (e.g. p. 549)). Sigmund, C., June 2000 (Arterioscler. Thromb. Vasc. Biol., p. 1425-1429, IDS), reports that variation in the genetic background contributes to unpredictable resulting phenotypes of transgenic or gene-targeted animals. "Animals containing the same exact genetic manipulation exhibit profoundly different phenotypes when present on diverse genetic backgrounds, demonstrating that genes unrelated, per se, to the ones being targeted can play a significant role in the observed phenotype" (e.g. abstract). Sigmund further states that "many of the phenotypes examined in transgenic and knockout models are influenced by the genetic background in which they are studied...Although all mouse strains contain the same collection of genes, it is allelic

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variation...and the interaction between allelic variants that influence a particular phenotype.

These “epigenetic” effects can dramatically alter the observed phenotype and therefore can influence or alter the conclusions drawn from experiments” (e.g. introduction).

In addition, Houdebine, L-M., 2002 (Journal of Biotechnology, Vol. 98, p. 145-160, IDS) points out that reintegration of an isolated gene into the genome of an animal by gene microinjection may generate complex and unpredictable biological situations (e.g. p. 146, first paragraph). Lee et al., 1999 (Neuron, Vol. 24, No. 3, p. 507-510, IDS) reports that “[e]arly efforts to produce animal models with tau pathologies were based on the expectation that TG mice that developed amyloid plaques would be good models of AD...but tau positive NTFs were never observed...neron loss was not detected in these APP TG mice even when they aged” (p. 508, right column, last paragraph). “Efforts to produce animal models of tau pathologies by directly overexpressing the tau gene have been limited” (p. 509, left column). The author produced transgenic mice overexpressing 3Rtau but fails to induce tangles identical to neurofilament tangles (NFTs) (p. 509, right column, second paragraph). The resulting phenotype of a transgenic mouse expressing all six human-tau isoforms, with or without the expression of endogenous mouse tau, could vary because of the different ratio of the isoforms expressed in said mouse. It is noted that the neuropathology of the disclosed genomic human-tau transgenic mouse is essentially normal, however, the hTau mice, which express six human tau isoforms but does not express mouse tau, show an accumulation of abnormal tau in the cell bodies and dendrites of neurons, tau phosphorylation and tau conformation change. This further strengthens the notion that the resulting phenotype of the claimed transgenic mouse was unpredictable at the time of the invention. Furthermore, the claimed transgenic mouse expressing all six human-tau

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isoforms as discussed above fails to correlate to any abnormal spinal cord pathology, any motor abnormality, or any neurodegenerative disease.

In view of the inherent unpredictability of the resulting phenotypes of the claimed transgenic mouse, the lack of evidence for any correlation with a particular disease and disorder, and the difficulty of producing animal models with tau pathologies, one skilled in the art at the time of the invention would not know how to make and/or use the claimed transgenic mouse.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the level of ordinary skill which is high, the amount of experimentation necessary, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 12 and 17 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: how the DNA sequence encoding human tau is introduced into a mouse and whether the human tau is expressed in the transgenic mouse. The method step fails to refer back the preamble of the claimed method, i.e. expression of human tau in a mouse.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 10-12 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Duff et al., 2000 (Neurobiology of diseases, Vol. 7, p. 87-98).

Claims 10-12 and 17 are directed to a transgenic mouse whose genome stably comprises a human genomic DNA sequence comprising a human tau promoter and a DNA sequence encoding human tau, wherein said DNA sequence comprises one SrfI restriction site in the tau coding region and the transgenic mouse expresses six isoforms of the human tau and the ratio of the six isoforms is altered in the transgenic mouse relative to the ratio in human, the progeny of said transgenic mouse, and a method of expressing human tau in a mouse. Claim 17 specifies the human tau isoform has an abnormal conformation.

Duff teaches generation of transgenic mice overexpressing a tau transgene derived from a human PAC and all six isoforms of human tau are expressed and distributed in neuritis and at synapses but is absent from cell bodies (e.g. abstract). Duff reports that there is a SrfI restriction site within the coding region of the human tau gene (e.g. bridging left and right column, p. 88). Duff teaches that “the representation of human tau isoforms in mouse brain tissue is very similar to that seen in human brain except that 3R tau is more abundant” and MC1 antibody that recognizes human tau with abnormal conformation changes also recognize the human tau protein

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in the generated transgenic mice (e.g. p. 95, left and right column). Thus, claims 10-12 and 17 are anticipated by Duff.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

17. Claims 10-12 and 17 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Refolo et al., October 1999 (Society for Neuroscience Abstracts, Vol. 25, No. 1-2, pp. 790, IDS).

Claims 10-12 and 17 are directed to a transgenic mouse whose genome stably comprises a human genomic DNA sequence comprising a human tau promoter and a DNA sequence encoding human tau, wherein said DNA sequence comprises one SrfI restriction site in the tau coding region and the transgenic mouse expresses six isoforms of the human tau and the ratio of the six isoforms is altered in the transgenic mouse relative to the ratio in human, the progeny of

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said transgenic mouse, and a method of expressing human tau in a mouse. Claim 17 specifies the human tau isoform has an abnormal conformation.

Refolo teaches generation of a transgenic mouse over-expressing the whole human tau gene. The human tau-gene transgenic mice express all six of the human tau proteins mRNA by RT-PCR analysis and Western blot analysis. The tau promoter-driven transgene is expressed most prominently in the pyramidal cell layer of the cortex and hippocampus and in the neuronal processes. Since the whole human tau gene was used to generate tau-gene transgenic mice, the SrfI restriction site is inherently present in said entire human tau gene. Since the claims do not specify how the ratio of the six isoforms is altered and the same whole human tau gene has been used to generate the transgenic mouse, it is inherent to the transgenic mouse generated by Refolo that said mouse also has altered ratio of the six isoforms of human tau. Although Refolo does not specifically teach producing offsprings of the heterozygous or homozygous human-tau transgenic mice, however, it was well known in the art to mate heterozygous transgenic mice to generate homozygous transgenic mice or to mate the homozygous transgenic mice to produce the next generation of transgenic mice. Thus, it would have been obvious for one of ordinary skill in the art at the time of the invention to produce progeny of the transgenic mice of claim 10 with reasonable expectation of success. Thus, claims 10-12 and 17 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Refolo.

Conclusion

Claims 2, 3, 7, 10-12 and 17 are rejected. Claims 1, 8 and 9 are in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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Shin-Lin Chen, Ph.D.

A handwritten signature in black ink, appearing to read 'SL Chen'.

**SHIN-LIN CHEN
PRIMARY EXAMINER**